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PHARMACOKINETICS OF LINCOMYCIN FOLLOWING SINGLE INTRAMUSCULAR ADMINISTRATION IN GOATS

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ABSTRACT

Pharmacokinetics of Lincomycin following intramuscular administration at dose rate 10 mg/kg body weight was investigated in healthy goats. Blood samples were collected from 1 min to 24 h of drug administration. The disposition of Lincomycin followed two compartment open model and drug was detected in plasma up to 8 h. The peak plasma concentration (C_{max}) was observed 5.63 ± 2.50 µg.ml^{-1}at 0.20 ± 0.16 h (T_{max}) after intramuscular injection of Lincomycin. Absorption half life ($t_{1/2ka}$) was very short (0.05 ± 0.01 h) indicated faster absorption of drug and low value of the distribution coefficient (1.50±0.36 h^{-1}) showed slow distribution from blood to tissues. The high AUC (33.8±7.68µg.h/mL) indicated good antibacterial activity of Lincomycin. The elimination half life, volume of distribution and total body clearance were 6.19±0.25 h, 2.95±0.50L/kg and 0.52±0.24L/h/kg, respectively. The long elimination half life indicated drug retain for longer period in body. Based on results, Lincomycin is suggested to be repeated at 12 h interval for organisms are sensitive to Lincomycin having MIC up to 0.6 µg/mL.

KEYWORDS: Pharmacokinetics, Lincomycin, Intramuscular & Goats

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Original Article

INTRODUCTION

Lincomycin is an antibiotic belongs to Lincosamide group. The main clinical indications of Lincomycin are acute and chronic respiratory tract infection, sinusitis, skin, soft tissue, bone and joint infections, septicaemia and endocarditis. It has the ability to penetrate tissues of poor vascularity, effective in the presence of pus and has shown positive response in cattle, sheep and horses (Plenderleith, 1988). Lincomycin is recommended in dogs and cats for the treatment of gram positive aerobic and anaerobic bacteria, especially against penicillin-resistant strains of *Staphylococcus* spp. and *Streptococcus* spp. (Giguere, 2006; Papich and Riviere, 2009). It has been suggested for potential use in cattle in combination with other antibiotics for susceptible infections that more commonly used medications or anaerobes, including *Bacteroides fragilis* (USP, 2008). For domestic animals, lincomycin used as an alternative to other antibiotics (Collignon *et al.*, 2008) and also for the treatment of respiratory tract infections in sheep, goats and calves (Papich and Riviere, 2009). Successful treatment of arthritis and pedal osteomyelitis usually associated with *Trueperella pyogens* (*Arcanobacterium pyogens*) has been reported with lincomycin in sheep (Giguere, 2013). Minimum inhibitory concentrations (MIC90) of lincomycin have been reported as 0.06-2.0µg.ml^{-1}against *Streptococcus*, *Mycoplasma hyopneumoniae,* and *Staphylococcus* spp. (Petinaki *et al.*, 2008; Albarellos *et al.*, 2012, Giguere, 2013). Pharmacokinetic studies have been conducted in dairy cattle (Weber *et al.*, 1981), calves (Burrows *et al.*, 1983, 1986), pigs (Chaleva and Nquyen, 1987), cats (Albarellos *et al.*, 2012) and buffalo calves (Gouri *et al.*, 2014). However, there is lack of data available for goats. Therefore the present study

was conducted to investigate the pharmacokinetics of lincomycin following single intramuscular administration in goats.

MATERIAL AND METHODS

Animals

The experiments were performed on six healthy female goats of 16-24 months age and weighing between 35-50 kg, procured from University dairy farm. The animals were acclimatized in the animal shed of department under uniform conditions for 2 weeks prior to the commencement of study. During this period, all animals were subjected to regular clinical examination and treated with anthelmintics for deworming. The animals were maintained on green fodder and wheat straw and water was provided *ad libitum*. The study was approved by the Institutional Animal Ethics Committee of Guru Angad Dev Veterinary and Animal Sciences University, India (vide Ref No. VMC/2014/IAEC/1046-73 dated 07-04-2014).

Drug Administration and Blood Sampling

Lincomycin was administered as single IM injection to all healthy animals at the dose rate 10 mg/kg body weight. Blood samples (3-5 ml) were drawn by venepuncture from the contralateral jugular vein at 0, 1, 2.5, 5, 10, 15, 30 min and 1, 2, 4, 8, 12 and 24 h. All were collected into heparinized test tubes and plasma from the samples were separated by centrifugation at 2500 rpm for 15 min and stored at -20 °C until drug assay.

Drug Assay

The drug was estimated by HPLC (Perkin Elmer, series 200) using the method of Nielsen and Gyrd-Hansen, (1998) by reverse – phase chromatography with analytical C18 column (particle size 5µ, 4.6×250mm, Waters, USA), acetonitrile as mobile phase A (25%), phosphate buffer as mobile phase B(75%), flow rate of 1 ml/ min, UV/VIS detector set 210 nm and Total Chrome software (version 6.1) for instrument control and data analysis.

Retention time of lincomycin was 7 min and calibration curve was linear between 0.5 and 100 µg/mL(r = 0.998, data not presented). The limits of detection and quantification were 0.1 and 0.5µg/ mL, respectively. Extration recoveries of lincomycin from plasma were 84.0±4.56, 90.7±4.12, and 94.9±3.29% for low, medium and high QC samples, respectively. Accuracy and precision were evaluated with QC samples at concentrations of 0.5, 5 and 25µg/mL. Intra and inter-day assay precision levels were lower than 5 and 6%, respectively.

Sample Processing

The plasma samples (2000 µl) were added to centrifuge tubes. Subsequently, to all samples, 2.3 ml of acetonitrile was added and mixed for 10 seconds (s) and the samples were centrifuged at 2500 rpm for 10 min. After centrifugation, 3600 µl of clear supernatant was pipetted into a fresh test tubes, and kept for evaporation, then evaporated samples were reconstitute with 400 µl of water and mixed for 10 s, and the mixed clear supernatant (200 µl) was pipetted into an autosampler vial.

Pharmacokinetic Analysis

Appropriate pharmacokinetic model was determined by visual examination of individual concentration time curves and by application of Akaike´s Information Criterian (AIC). The mean pharmacokinetic variables were obtained by averaging the variables for drug disposition from individual animals. The pharmacokinetic parameters were calculated according to classical equation (Gibaldi and Perrier, 1982). The mean pharmacokinetic variables were obtained by

averaging the variables calculated for drug disposition after IM route of administration to each animal. The time for which the plasma drug levels remain above or equal to minimal inhibitory concentration (MIC) value is calculated using the formula:

$$\%T>MIC = \ln\left[\frac{D}{Vd(area) \times MIC}\right] \times \left[\frac{t_{1/2\beta}}{\ln(2)}\right] \times \left[\frac{100}{DI}\right]$$

Where T>MIC is the time interval (in percent) during which the plasma concentration is above or equal to the MIC values, ln is natural logarithm, D is the proposed dose, $V_{d(area)}$ is the volume of distribution, $t_{1/2\beta}$ is the terminal elimination half-life, and DI is the dose interval (Turnidge, 1998).

RESULTS AND DISCUSSIONS

Various kinetic determinants that describe the distribution and elimination pattern of lincomycin after its intramuscular injection were calculated and presented in Table 1. The disposition curve following IM route of administration revealed that pharmacokinetics of lincomycin followed two-compartment open model (Figure 1). The peak plasma concentration (C_{max}) was observed 5.63 ± 2.50 µg.ml^{-1}at 0.20 ± 0.16 h (T_{max}) in healthy goats. Table 2 shows the calculated % T>MIC for lincomycin based on the estimated pharmacokinetic parameters obtained following IM injection in healthy goats for 8, 12 and 24 h dosing interval.

The plasma disposition of lincomycin followed two compartment open model. Absorption half life ($t_{1/2ka}$) in the present study was very short (0.05 ± 0.01 h) denoting faster absorption of drug *via* IM route. Similar value for absorption half life ($t_{1/2ka}$= 0.04±0.05 h) of lincomycin was observed in cat following IM injection (Albarellos *et al.*, 2012).

The value of AUC of lincomycin in goats was (33.8±7.68 µg.ml^{-1}.h) indicating good antibacterial activity of the drug. The high value of AUC obtained in the present study was consistent to the high value reported for AUC of lincomycin in cats 31.01 ±6.74 µg.ml$^{-1\cdot}$h. (Alberallos *et al.*, 2012).

The volume of distribution relates to amount of drug in the body in relation to amount present in blood. The large Vd_{area} (2.95 ± 0.51L.kg^{-1}) indicated good distribution of lincomycin in various body fluids and tissues of goats. The lipophilic nature and high pK_a values of 7.6 of this compound might be the major reasons for the good distribution of lincomycin to the tissues.

Total body clearance of lincomycin, which represents the sum of metabolic and excretory process in goats was 0.52 ± 0.24 L.kg^{-1}.h^{-}1.The elimination half-life in the present study was longer (6.09 ±1.67 h) as compared the $t_{1/2\ \beta}$ of lincomycin 3.67±1.32 h in cats following IM route of administration (Albarellos *et al.*, 2012).The value of MRT was 8.98 ± 2.34 h in goats which was higher than the value of MRT (5.15±1.66 h) of lincomycin in cats following IM administration.

Minimum inhibitory concentration (MIC_{90}) lincomycin has been reported as 0.06-2.0 µg.ml^{-1}against *Streptococcus, Mycoplasma hyopneumoniae,* and *Staphylococcus* spp. (Petinaki *et al.*, 2008; Albarellos *et al.*, 2012; Giguere, 2013). The T>MIC has been calculated for MIC_S of 0.06, 0.1, 0.6 and 1µg/mL.

Lincomycin acts as time dependant antibacterial drug. The most important pharmacodynamics/pharmacokinetic parameter for this type of drug is length of time during which drug remains above the MIC value. It is generally

recommended that T>MIC should be atleast 50% of the dosage interval to ensure an optimal antibacterial effect (Toutain and lees, 2004). The purpose of present study was to calculate and modify the dosage regimen of linomycin in healthy goats following IM administration. The experiment data in present study, was shows that lincomycin at dose rate 10 mg/kg body weight should be repeated at 12 h interval for that organism which are sensitive to lincomycin having MIC up to 0.6 µg/mL.

CONCLUSIONS

The dosage regimen suggested in present study may be considered for clinical use in goats after establishing PD studies and potential clinical testing of lincomycin in this species. Since only six animals were used in the present study, the PK parameters need to be verified in a larger population of goats and variations in dosage regimens may be required.

CONFLICT OF INTEREST

None of the authors has any financial or personal relationships with other people or organisations that could inappropriately influence or bias the content of the paper.

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APPENDICES

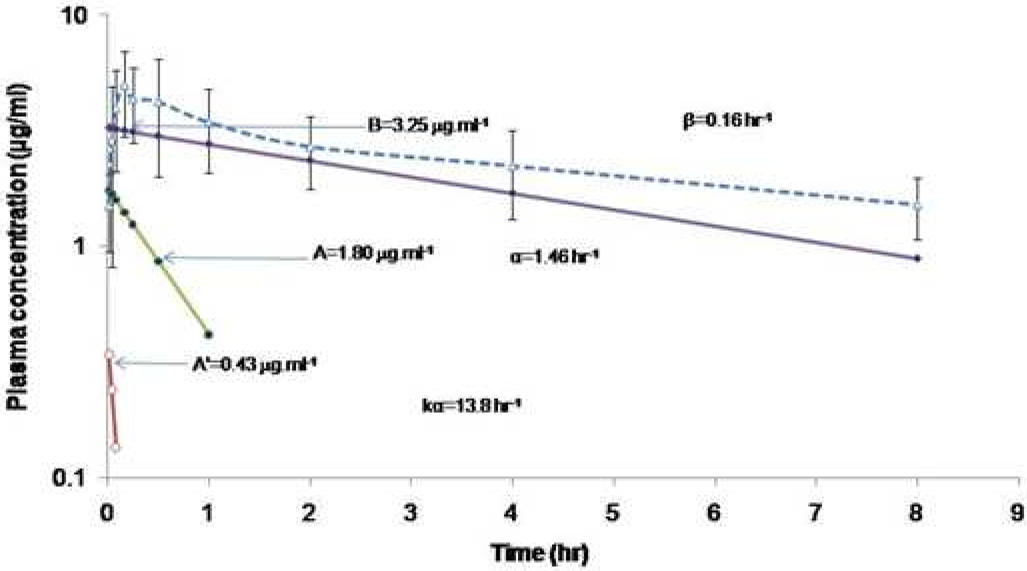

Figure 1: Plasma Concentration Time Profile of Lincomycin in Healthy Goats following Single IM Administration at dose of 10 mg.kg^{-1}. Distribution (---○---) and Elimination Phases (-----------) are Represented by Least Square Regression Lines. Plasma Concentrations at different Time Intervals are represented by Dots (♦)

Table 1: Disposition Kinetics of Lincomycin following its Single Intramuscular Injection (10 mg.kg^{-1}) in healthy Goats$^{=6}$

Parameter	Unit	Mean ± SE
A	µg.ml^{-1}	1.80± 0.17
$t_{½}$ka	h	0.05± 0.01
α	h^{-1}	1.50±0.36

Table 1: Contd.,		
$t_{½\alpha}$	h	1.63±1.15
K_{12}/k_{21}	Ratio	0.36±0.08
AUC	µg.ml^{-1}.h	33.8±7.68
$V_{d(area)}$	L.kg^{-1}	2.95±0.51
B	µg.ml^{-1}	3.25±0.53
β	h^{-1}	0.16±0.04
t½β	h	6.09±1.67
$t½_{kel}$	h	4.33±1.19
Cl_B	L.kg^{-1}.h^{-1}	0.52±0.24
MRT	h	8.98±2.34

A, zero time intercept of distribution phase; $t_{½}$ka, absorption half life; α, distribution rate constant; $t_{½\alpha,}$ distribution half life; $K_{12}/K_{21,}$ ratio of rate constant for central to peripheral compartment and peripheral to central compartment; AUC, area under concentration; $V_{d(area),}$ volume of distribution; B, zero time intercept of elimination phase; β, elimination rate constant; $t_{½\beta}$, elimination half life; $t_{½kel,}$ elimination half life from central compartment; $Cl_{B,}$ total body clearance; MRT mean residence time of the drug in body.

Table 2: Calculated %T>MIC for Lincomycin based on the Estimated Pharmacokinetic Parameters Obtained following IM Injection in Healthy Goats for 8, 12 and 24 h Dosing Interval

MIC(µg/ml)	T>MIC		
	24	**12**	**8**
0.01	187	373	560
0.06	121	242	363
0.1	102	205	307
0.6	37	74	111
1	18	36	54

T>MIC has been calculated for MIC 0.06, 0.1, 0.6, and1µg/mLon the basis of reported MIC_{90} (0.06-2.0 µg/mL) against *Streptococcus*, *Mycoplasma hyopneumoniae*, and *Staphylococcus* spp.(Petinaki et al., 2008; Albarellos et al., 2012; Giguere, 2013).